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Hoben, Ashley D.; Buunk, Abraham P.; Fincher, Corey L.; Thornhill, Randy; Schaller, Mark

Published in:
Evolutionary Psychology

DOI:
[10.1177/147470491000800408](https://doi.org/10.1177/147470491000800408)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Hoben, A. D., Buunk, A. P., Fincher, C. L., Thornhill, R., & Schaller, M. (2010). On the Adaptive Origins and Maladaptive Consequences of Human Inbreeding: Parasite Prevalence, Immune Functioning, and Consanguineous Marriage. *Evolutionary Psychology*, 8(4), 658-676.
<https://doi.org/10.1177/147470491000800408>

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Original Article

On the Adaptive Origins and Maladaptive Consequences of Human Inbreeding: Parasite Prevalence, Immune Functioning, and Consanguineous Marriage

Ashley D. Hoben, Department of Psychology, University of Groningen, Groningen, The Netherlands. Email: a.d.hoben@rug.nl (Corresponding author).

Abraham P. Buunk, Royal Netherlands Academy of Arts and Sciences and Department of Psychology, University of Groningen, Groningen, The Netherlands.

Corey L. Fincher, Department of Biology, University of New Mexico, Albuquerque, NM, USA.

Randy Thornhill, Department of Biology, University of New Mexico, Albuquerque, NM, USA.

Mark Schaller, Department of Psychology, University of British Columbia, Vancouver, BC, Canada.

Abstract: We propose that consanguineous marriages arise adaptively in response to high parasite prevalence and function to maintain coadapted gene complexes and associated local adaptation that defend against local pathogens. Therefore, a greater prevalence of inbreeding by consanguineous marriage is expected in geographical regions that historically have had high levels of disease-causing parasites. Eventually such marriages may, under the contemporary high movement of people with modern transportation, jeopardize the immunity of those who practice inbreeding as this leads to an increased susceptibility to novel pathogens. Therefore, a greater frequency of inbreeding is expected to predict higher levels of contemporary mortality and morbidity from infectious diseases. This parasite model of human inbreeding was supported by an analysis involving 72 countries worldwide. We found that historically high levels of pathogen prevalence were related positively to the proportion of consanguineous marriages, and that a higher prevalence of such marriages was associated with higher contemporary mortality and morbidity due to pathogens. Our study addresses plausible alternative explanations. The results suggest that consanguineous marriage is an adaptive consequence of historical pathogen ecologies, but is maladaptive in contemporary disease ecologies.

Keywords: consanguineous marriages, cousin marriage, inbreeding, infectious disease, parasite prevalence

Introduction

Consanguineous marriage is marriage that occurs between genetically close relatives such as cousins (Thornhill, 1991). Despite the presumed negative effects for offspring produced from this type of marriage (e.g., inbreeding depression), it continues to occur at substantially high rates in various parts of the world and typically involves various categories of cousins, and, in some cases, uncle–niece unions (e.g., Rao and Inbaraj, 1977). Consanguineous marriage is especially common among Muslim and Hindu populations in Africa and Asia (Jaber, Halpern, and Shohot, 1998). The prevalence of consanguineous marriages varies throughout the world. Rates of 50% and higher are found in countries such as Jordan, Kuwait and Saudi Arabia (Jaber, Shohot, and Halpern, 1996), while on the other hand, rates are between 0% and 9% in the United States (Jaber et al., 1998), Japan (Imaizumi, 1986; Schull, Nagano, Yamamoto, and Komatsu, 1970), and Brazil (Freire-Maia, 1989).

There are multiple factors that may account for these cross-cultural differences in the frequency of consanguineous marriage (Thornhill, 1991; Joseph, 2007). In areas of relatively low socioeconomic levels, consanguineous marriage may help facilitate marriage among the poor because it allows them to avoid payments that are traditionally associated with marriage, such as a dowry or bride wealth. For the more prosperous, marrying cousins may keep familial wealth together by preventing land and other wealth from distribution outside of the family which may maintain or increase the status and power of the family in society. For these reasons, across many different cultures, parents tend to prefer mates for their children who come from the same ethnic and religious group, and marrying a cousin may represent an enhanced expression of this preference (Buunk, Park, and Dubbs, 2007; Buunk, Park and Duncan, 2010). In addition, marrying a cousin may facilitate the transition for a woman to her husband's family, and may allow a woman to maintain ties with her natal family. Finally, geographical isolation may play a role. In small, isolated populations, individuals have limited access to mates except from within their group, increasing the frequency of consanguineous marriage.

To complement those partial explanations for the persistence of consanguineous marriages, in the present research we offer an additional explanation that we label the “parasite hypothesis of inbreeding.” This hypothesis suggests that inbreeding can serve as an adaptive defense against local parasite genotypes, and thus is more prevalent in geographical regions that, historically, have had relatively higher levels of disease-causing pathogens (i.e., parasites that lead to infectious diseases). Adaptation to *local* parasites, however, comes at a cost: increased susceptibility to *novel* parasites. Novel parasites are encountered increasingly as modern transportation brings human groups that were traditionally geographically inaccessible into contact. Hence, the parasite hypothesis of inbreeding predicts that inbreeding in contemporary settings is frequently maladaptive.

The adaptiveness of avoiding inbreeding

The fitness costs associated with inbreeding are well-discussed in the literature. In general, it is assumed that inbreeding reduces fitness, and that outbreeding is adaptive because it fosters the genetic diversification of offspring in order to combat ecological

adversity, including hostile biological factors such as parasitic diseases (Hamilton, Axelrod, and Tanese, 1990; Ridley, 1993; Trivers, 1985). The negative effects of inbreeding have been documented in many non-human species. Evidence of the negative influence of inbreeding on survival, both in the early and late stages of life, has been found, for example, in bird species including the collared flycatcher, great tit, great reed warbler and blue tit (see Kempenaers, 2007, for a review). Furthermore, a positive relationship between inbreeding and parasite load also has been found in non-human species. For example, in California sea lions, it was found that more inbred individuals had a larger variety of helminth infections (Acevedo-Whitehouse, Gulland, Grieg and Amos, 2003; see Kempenaers, 2007, for further review).

Humans have encountered parasites throughout their evolutionary history and possess many immune system adaptations for defence against them. Human pathogen-defence adaptations are imperfect because parasites and hosts evolve antagonistically. Parasites often evolve quickly to challenge a host species' immune-system adaptations. When hosts lag behind parasite adaptations, the more genetically homogenous a group is, the quicker an infection can spread. Consequently, this may have created selection pressure for behaviors that increase genetic diversity within a population, and as a result, individuals who avoided mating with genetically close kin would have been more reproductively successful. Accordingly, humans exhibit psychological and behavioral adaptations that function to prevent mating with very close relatives (Lieberman, 2007). One prediction that emerges from this perspective is that infectious-disease-related morbidity and mortality is more prevalent in contemporary populations with a history of inbreeding, compared to outbred populations. Indeed, Lyons, Frodsham, Zhang, Hill and Amos (2009) provided evidence that suggests that the more inbreeding occurs in a population, the greater the susceptibility to certain infectious diseases (particularly, tuberculosis and hepatitis B). This parasite-generated morbidity and mortality is a component of inbreeding depression. Another related component arises from the positive correlation between consanguinity and the sharing of rare deleterious recessive alleles between mates. Therefore, consanguineous marriage increases the probability (over outbreeding) of deleterious recessives being passed onto offspring, resulting in a higher prevalence of infectious disease among individuals who are homozygous for deleterious recessives (Bittles and Neel, 1994).

The adaptiveness of inbreeding

Although the negative fitness effects of consanguineous marriages are widely recognized, inbreeding may have fitness-enhancing consequences as well. Within the non-human literature, there is evidence that inbreeding can have positive effects on immunity. For example, among decorated crickets (*Gryllodes sigillatus*), inbred individuals have, on average, a better ability to encapsulate foreign bodies than outbred individuals, which suggests an enhanced ability to deal with invading parasites (Gershman et al., 2010). It also has been found that colonies of dampwood termites (*Zootermopsis angusticollis*) started by pairs of nestmates (close relatives) have significantly higher survival rates than colonies started by pairs of non-nestmates (Rosengaus and Traniello, 1993).

Among humans, two different lines of argument link fitness benefits to inbreeding. One view relates inbreeding to fertility, as fertility has been shown to increase among

women married to genetic relatives. However, this result may be due, in part, to the younger age at which women in consanguineous unions tend to have their first live birth (Jaber et al., 1998). Additionally, it has been argued that involuntary sterility and prenatal losses are reduced in consanguineous couples because of the increased genetic compatibility between mother and fetus. It is possible that the greater fertility among consanguineous couples may be a compensatory mechanism for increased postnatal deaths (Bittles, 2001; Schull and Neel, 1972; Tuncbilek and Koc, 1994). Despite this evidence, the inbreeding and fertility linkage is far from clear, and there is also reason to expect that fertility may actually be lower among consanguineous couples. It has been suggested that fetuses that have been conceived from parents who are histoincompatible (that is, fetuses that have paternally derived antigens that are different from the mother's) are less likely to result in spontaneous abortion; consequently, couples who share histocompatibility antigens (HLA) would tend to have reduced fertility (Ober, Elias, Kostyu, and Hauck, 1992). Lower fertility could also be attributed to the expression of deleterious genes that have a negative effect on early development and consequently lead to periconceptual losses (Ober, Hyslop and Hauck, 1999).

The second argument linking inbreeding to fitness benefits is more compelling, and it focuses on resistance to infectious disease. Although it has been argued that inbreeding is detrimental to immune function because it increases the possibility of homozygosity of alleles, actual empirical evidence for a heterozygotic advantage is mixed. In fact, specific homozygosities can actually confer resistance to specific diseases. For example, among humans, the α^+ -Thalassemia allele protects against malaria, and α^+ -Thalassemia homozygotes are less likely than other individuals to develop fatal forms of malaria (Allen, O'Donnell, and Alexander, 1997). Consequently, it has been argued that inbreeding may confer adaptive advantages under circumstances in which malaria-causing pathogens are endemic (Denic, Nagelkerke, and Agarwal, 2008; Denic and Nicholls, 2007). As well, individuals who are homozygotic for a defect on *CKR-5* seem to be resistant to the sexual transmission of HIV-1 (Liu et al., 1996). Effects such as these are not merely specific to humans. Evidence of a homozygotic advantage also has been found in water buffalos (*Bubalus bubalis*). One pathogen that has had severe consequences on herds of water buffalo is brucellosis, which causes spontaneous abortions. A study examining the genetic resistance to this particular pathogen found that being homozygous for the allele *Nramp1 B* was significantly and positively associated with resistance to this infection (Borriello et al., 2006). In another study on a species of fish, the rostrum dace (*Leuciscus leuciscus*), it was found that those dace that were either highly homozygous or highly heterozygous at the multilocus level had fewer ectoparasites, on average, than those that were of intermediate heterozygosity (Blanchet, Rey, Berthier, Lek, and Loot, 2009).

The evidence of a homozygotic advantage of certain alleles that confer resistance to specific parasitic diseases has implications for the adaptive value of inbreeding. Inbreeding would maintain the homozygosity of these alleles and be especially important in areas that are subjected to endemic occurrences of the particular diseases involved (e.g., Borriello et al., 2006). In turn, this would have implications for the distribution of human inbreeding, specifically cultural customs that promote the marriage between relatives. These customs would potentially increase the likelihood that offspring resulting from these unions also

would inherit any homozygotic advantage.

The parasite hypothesis of inbreeding

The evidence reviewed above suggested that, while inbreeding can have deleterious consequences for anti-parasite defense, it may also have specific positive consequences for anti-parasite defense. The negative consequences result primarily from reduced variation in the molecular milieu (perhaps especially major histocompatibility variation) from which an individual can mount an immune response (Penn and Potts, 1999). This results in decreased resistance especially towards novel pathogens. In contrast, the positive consequences of inbreeding result from regionally localized host–parasite co-evolution which maintains co-adaptive gene complexes that confer superior immunological defense against endemic (but not exotic) parasite genotypes (Shields, 1982).

Compared to contemporary societies with their high levels of dispersal and intermixing, human populations during pre-industrial epochs were relatively unlikely to come into contact with novel parasites. Under low intergroup dispersal of parasites, the immunological benefits of inbreeding (i.e., co-adapted gene complexes conferring resistance to local parasites) may have outweighed the immunological costs (i.e., reduced resistance to novel parasites). These benefits of inbreeding most likely outweighed the costs within ecologies in which endemic pathogens were more prevalent.

This has a clear implication for cultural differences in marriage behavior. Individual behavioral tendencies and cultural norms promoting consanguineous marriages most likely emerged in geographical regions that historically were characterized by high pathogen prevalence. This hypothesis is supported by evidence indicating a positive correlation between malaria endemism and the frequency of consanguineous marriages (Denic and Nicholls, 2007). That evidence, however, is specific to just one of the many human infectious diseases that historically have been of differential prevalence worldwide. Previous research has not addressed many of the alternative explanations for the observed correlation. In the study reported below, we tested more rigorously the hypothesis that the *historical* prevalence of pathogens would uniquely predict contemporary cross-cultural differences in the frequency of consanguineous marriages.

Additionally, we tested the second part of the parasite hypothesis of inbreeding that pertains to the immunological consequences of inbreeding within contemporary societies. In contrast to the relative isolation of different human populations during historical epochs, individuals living in contemporary human societies are much more likely to come into contact with novel pathogens to which there is no, or limited, local adaptive immunity. This is because recent technological advances have facilitated travel and migration around the globe leading to an increased globalization of infectious disease (Smith, Sax, Gaines, Guernier, and Guégan, 2007). Moreover, humans live in larger and denser populations today than were experienced throughout much of human history, providing the necessary conditions for the maintenance of a diverse set of pathogens and the emergence of novel pathogens (Dobson and Carper, 1996; Guégan and Constantin de Magny, 2007; Wilcox, Gubler, and Pizer, 2008). Under these contemporary circumstances, populations characterized by higher levels of inbreeding are more vulnerable to new infectious diseases. Hence, while consanguineous marriage practices may historically have been adaptive

within ecologies characterized by the high prevalence of mainly endemic pathogens, in contemporary ecologies the maladaptive consequences of inbreeding, (i.e., a decreased resistance to novel pathogens) may predominate, resulting in higher mortality and morbidity. Therefore, the second prediction is that, across countries, a higher incidence of consanguineous marriages predicts increased *contemporary* mortality and morbidity due to infectious diseases.

Materials and Methods

Prevalence of consanguineous marriage

Contemporary geopolitical regions served as the units of analysis. Bittles (1998) provided a compilation of the proportion of consanguineous marriages (those between persons genetically related as second cousins or closer, which is equivalent to a coefficient of inbreeding ≥ 0.0156) within geopolitical regions based primarily on refereed journal articles supplemented with data from book chapters, submitted manuscripts, and personal communications. Bittles (2001) summarized these data and discussed the global patterns in relation to clinical genetics. As a basis, Bittles' report (1998) references 381 surveys that include information for 6.55 million marriages. We collected these data from www.consang.net in October 2010. This gave us data on the proportion of consanguineous marriages in 72 different geopolitical regions. Multiple estimates were provided for many of these regions, and, in these cases, we computed the mean percentage of consanguineous marriages by weighting the individual estimates according to sample size.

For most of the countries in our analysis, it was also possible to compute a mean coefficient of inbreeding within the population (based also on values obtained from www.consang.net). For two reasons the coefficient of inbreeding would seem to be a less appropriate metric for testing our hypotheses. First, it has been argued that the coefficient of inbreeding may be a poor estimate of the proportion of alleles that are shared between individuals from a common ancestor (Markert et al., 2004). Second, compared to the percentage of consanguineous marriages, the coefficient of inbreeding is an abstract concept that exists separate from the actual *behavioral* adaptation to which the parasite hypothesis of inbreeding pertains. That is, our hypothesis focuses on individual behavioral inclinations (and societal structures that promote those inclinations) toward the selection of consanguineous mates. In contrast, the coefficient of inbreeding assesses, indirectly, a population-level byproduct of those behavioral inclinations. For this reason, our primary analyses focused on the percentage of consanguineous marriages within each country.¹

¹ Although the primary analyses focused on the percentage of consanguineous marriages, we conducted a set of ancillary analyses that focused on the coefficient of inbreeding instead. The results are largely the same. For example, supporting the primary hypothesis, historical pathogen prevalence predicts the weighted mean coefficient of inbreeding ($r = 0.385$; $p = 0.001$), and this effect remains significant ($\beta = 0.362$, $p = 0.003$) even when statistically controlling for GDP per capita in a regression analysis. In general, while analyses focusing on coefficient of inbreeding (rather than on percentage of consanguineous marriage) tend to produce slightly weaker effect sizes, the nature of these effects is identical to those reported in the Results section below, and the implied conclusions are the same.

Historical pathogen prevalence

An overall index of historical pathogen prevalence was computed, using methods identical to those reported in previous investigations into the relation between historical pathogen prevalence and cross-cultural differences (Fincher, Thornhill, Murray, and Schaller, 2008; Murray and Schaller, 2010; Murray, Trudeau, and Schaller, in press; Schaller and Murray, 2008). In brief, for each geopolitical region, the historical prevalence rates of nine debilitating pathogenic diseases (dengue, filariae, leprosy, leishmanias, malaria, schistosomes, trypanosomes, tuberculosis, and typhus) were estimated on the basis of old atlases of infectious diseases and other historical epidemiological information that describe disease severity back to the early 1900s. The nine individual prevalence estimates were standardized (transformed into z-scores), and the mean of these nine standardized scores was computed to serve as the estimate of the historical prevalence of pathogens in each nation. For four of these 72 regions (indicated with an asterisk in the Appendix), historical data on either leprosy and/or tuberculosis were unavailable; for these regions, the overall pathogen prevalence index was computed as the mean z-score of the seven remaining diseases. (For additional details and for actual pathogen prevalence scores for each geopolitical region, see Murray and Schaller, 2010).

For the sake of comparison, we computed a second measure of pathogen prevalence, based on contemporary epidemiological data obtained from the Global Infectious Diseases and Epidemiology Online Network (GIDEON; www.gideononline.com; for details and validation see Fincher and Thornhill, 2008b, and Fincher, Thornhill, Murray, and Schaller, 2008; Fincher and Thornhill, 2008b includes these data). Consistent with prior inquiries of cross-cultural variation (Fincher et al., 2008; Murray and Schaller, 2010; Schaller and Murray, 2008), our results indicated that this measure of contemporary pathogen prevalence was less effective than historical pathogen prevalence in predicting the frequency of consanguineous marriages. This pattern of results is consistent with the hypothesis that consanguineous marriage is a consequence, rather than a cause of, pathogen prevalence. In the results presented below, we focus on the predictive consequences of historical pathogen prevalence.

Contemporary morbidity and mortality from parasites

To assess the extent to which individuals within different nations suffer from death and debilitation as a consequence of infectious diseases in contemporary societies, we used an index provided by the World Health Organization (WHO, 2004). The index of Disability Adjusted Life Years (DALY) – available for 69 of the 72 regions in our dataset – combines into a single measure the extent to which infectious diseases contribute to morbidity and mortality within a nation, adjusted for country-wide population size (one DALY unit equals a one-year reduction in healthy life specifically as a result of infectious disease, per 100,000 people). Higher values indicate more morbidity and mortality from the 28 diseases tracked by the World Health Organization for 2002 under their category of “infectious and parasitic diseases.” These scores were subjected to a natural log transformation to reduce skewness and kurtosis.

Other variables

In addition to these variables of primary conceptual interest, we assessed variables in order to address potential alternative causal explanations for the hypothesized relationships between historical parasite prevalence, consanguineous marriages, and contemporary, parasite-mediated morbidity and mortality. These variables are identified and discussed in the Results section below.

Results

Historical pathogen prevalence and frequency of consanguineous marriage

The first prediction was that historical pathogen prevalence would positively predict regional differences in the percentage of consanguineous marriages. This was indeed the case: across all 72 geopolitical regions in the correlation analysis, $r = 0.39$, $p = 0.001$ (see Table 1).

This analysis treats geopolitical regions – primarily nations – as the units of analysis. It can be argued that many geopolitical boundaries fail to correspond meaningfully to cultural boundaries. Therefore, we also computed values indicating the historical prevalence of pathogens and the percentage of consanguineous marriages within each of six world cultural areas identified by Murdock (1949), and conducted additional analyses in which we treated these six world regions as the units of analysis. Although the sample size of six is tiny, it is noteworthy that the correlation between pathogen prevalence and consanguineous marriage replicates the positive correlation observed in our primary analysis ($r = 0.56$). Thus, in cultural areas with a higher historical prevalence of pathogens, there is a higher frequency of consanguineous marriage.

There are various potentially confounding factors that may account for the correlation between historical pathogen prevalence and the occurrence of consanguineous marriage. Pathogen prevalence is correlated highly negatively with economic wealth within a region (see Fincher et al., 2008), and, as reviewed above, there are reasons to believe that economic poverty may facilitate the emergence and maintenance of consanguineous marriages. The positive correlation between pathogen prevalence and consanguineous marriages might, therefore, merely be a spurious result of a negative relation between economic wealth and consanguineous marriage. However, we found no compelling support for this alternative explanation. When historical pathogen prevalence and gross domestic product per capita (GDP per capita; 2009 data obtained from the CIA World Factbook, www.cia.gov) were jointly entered as predictors of consanguineous marriages, the effect of GDP per capita was weak and non-significant ($\beta = -0.172$, $p = 0.127$), while the effect of pathogen prevalence remained stronger than that of GDP per capita ($\beta = 0.371$, $p = 0.001$).

Recent evidence reveals that historical pathogen prevalence predicts cross-cultural differences in personality traits that may inhibit behavioral contact with novel people, places, and things (lower levels of extraversion and openness to new experiences; reduced willingness to engage in sex without commitment [sociosexuality]; Schaller and Murray, 2008). It might be argued that the effect of pathogen prevalence on consanguineous marriage might simply be a cultural by-product of these personality traits. However, we did not find evidence for this conjecture. We conducted a series of six regression analyses, each of which included historical pathogen prevalence and one additional trait variable as

predictors of consanguineous marriage. These regional variables included two indices each of both extraversion and openness from McCrae, Tarraciano, et al. (2005) and Schmitt et al. (2007), and indices of both male and female sociosexuality from Schmitt (2005). In none of those prior studies were the trait variables assessed for the entire sample of 72 regions included in our analysis; consequently, our analyses here were substantially restricted in sample size. Across all six analyses, the trait variables failed to emerge as significant predictors of consanguineous marriages (mean absolute values of β ranged from 0.028 to 0.274, p values ranged from 0.125 to 0.899). In contrast, substantial effects of pathogen prevalence emerged from five of the six analyses (β 's ranged from 0.341 to 0.566, p values ranged from 0.008 to 0.06). The one exception involved the index of female sociosexuality. But even for this one analysis in which the effect of pathogen prevalence failed to approach statistical significance, the magnitude of this effect still exceeded that of female sociosexuality (β 's = 0.333 and 0.194, respectively). Overall, there was no evidence to suggest that the percentage of consanguineous marriage across countries was simply a cultural by-product of personality traits predicted by pathogen prevalence.

Other recent evidence shows that pathogen prevalence predicts the emergence of collectivistic cultural ideologies that are conceptually defined by (and manifest in) strong extended family bonds, xenophobia, and neophobia more broadly (Fincher et al., 2008; Thornhill, Fincher and Aran, 2009). It is therefore instructive to test the extent to which the effect of pathogen prevalence on consanguineous marriage is independent of (versus possibly mediated by) its effects on cultural collectivism. We conducted two regression analyses, each of which included historical pathogen prevalence and an index of cultural collectivism as predictors of consanguineous marriage. The two analyses produced divergent results. In one analysis (using an index of collectivism reported by Gelfand, Bhawuk, Nishii, and Bechtold, 2004; $n = 36$), the unique effect of pathogen prevalence was reduced relative to the effect of collectivism (β 's = 0.134 and 0.232, respectively), suggesting that the effect of pathogen prevalence on the highly specific effect of consanguineous marriage may not be independent of its broader effects on collectivistic practices in general. In contrast, the other regression analysis (using a language-based indicator of collectivism reported by Kashima and Kashima, 1998; $n = 49$) revealed a negligible effect of collectivism and a substantial unique effect of pathogen prevalence ($\beta = 0.341$, $p = 0.06$.)

Finally, because it has been observed previously that consanguineous marriage is more common in regions in which malaria is endemic (Denic and Nicholls, 2007), it is important to determine if the effect we found is specific to malaria. That does not appear to be the case. We conducted a regression analysis in which the historical pathogen prevalence index was entered along with the specific prevalence of malaria as predictors of consanguineous marriage. Results indicated no unique effect of malaria prevalence ($\beta = 0.016$, $p = 0.92$), but the overall index of historical pathogen prevalence remained a significant predictor of consanguineous marriage ($\beta = 0.348$, $p = 0.037$).

In sum, historical pathogen prevalence was a significant predictor of regional differences in consanguineous marriages. Furthermore, this effect largely remains even when statistically controlling for a wide variety of additional variables that are associated with pathogen prevalence. These results are consistent with the hypothesis that regional

differences in consanguineous marriage emerged, in part, because consanguineous marriages conferred immunological resistance to local pathogens and that these adaptive benefits accrued primarily in geographical regions with high levels of pathogen prevalence.

Consanguineous marriage and immunological consequences in contemporary societies

The second hypothesis implies that, while inbreeding may have conferred immunological resistance to local pathogens, the associated reduction in genetic variability may retard immunological resistance to novel pathogens. Consequently, in contemporary societies, it was predicted that a higher frequency of consanguineous marriages will be associated with higher levels of morbidity and mortality due to infectious disease (as measured by the infectious disease DALY index). Clear support was found for this prediction: there was a substantial positive correlation between prevalence of consanguineous marriage and the DALY index, $r = 0.572$, $p = 0.001$.

Again, we examined if this correlation might be the spurious consequence of shared variance with other variables. The first of these is economic wealth. We conducted a regression analysis with both the prevalence of consanguineous marriage and GDP per capita as predictors of DALY. Results revealed that DALY was not predicted by GDP per capita ($\beta = -0.051$, $p = 0.640$), however the frequency of consanguineous marriage remained a unique predictor of DALY ($\beta = 0.517$, $p < 0.001$). Thus, national differences in economic wealth are unable to explain the association between the prevalence of consanguineous marriage and current pathogen prevalence.

This association might also be a spurious consequence of the fact that contemporary morbidity and mortality from infectious disease are highly correlated with historical pathogen prevalence. We conducted a regression analysis with both consanguineous marriage and historical pathogen prevalence as predictors of DALY. Results revealed that, even though DALY was substantially predicted by historical pathogen prevalence ($\beta = 0.583$, $p < 0.001$), the frequency of consanguineous marriage remained a unique predictor of DALY as well ($\beta = 0.312$, $p = 0.001$). A second regression analysis included both consanguineous marriage and contemporary pathogen prevalence (based on epidemiological data obtained from the GIDEON database) as predictors of DALY. Again, the prevalence of consanguineous marriage remained a unique predictor of DALY ($\beta = 0.340$, $p < 0.001$).

In sum, these results support our second hypothesis. In contemporary societies (in which contact with novel pathogens is relatively common), a higher percentage of consanguineous marriage is associated with increased morbidity and mortality due to infectious diseases. This relationship does not seem to be due to differences in economic wealth. Moreover, this effect occurs regardless of the historical prevalence of pathogens, which is consistent with the hypothesis that, while inbreeding may have had historically positive effects on local immunological resistance, it seems to negatively affect current resistance and associated fitness.

Discussion

The results supported both predictions derived from the parasite hypothesis of

inbreeding. Our first prediction was deduced from theory and evidence indicating that the increased homozygosity and other genetic coadaptation that results from inbreeding can facilitate highly specific forms of immunological resistance to local parasites, and that these immunological benefits will be most pronounced under ecological circumstances in which endemic pathogens are more highly prevalent (Denic et al., 2008; Denic and Nicholls, 2007; Fincher and Thornhill, 2008a, b; Shields, 1982). The implication is that regional differences in the historical prevalence of endemic infectious diseases will predict contemporary cross-cultural differences in the prevalence of consanguineous marriages. This appeared to be the case. These results complement and extend previous findings that focused just on the endemic prevalence of malaria (Denic and Nicholls, 2007). Further extending prior work, our results address alternative causal explanations. For instance, the causal priority of pathogen prevalence is implicated indirectly by the fact that consanguineous marriage is more strongly predicted by historical pathogen prevalence than by contemporary pathogen prevalence. Additional analyses indicated that the effect cannot be merely a spurious result of other variables (e.g., GDP per capita) that covary with pathogen prevalence, nor is it a cultural-level by-product of individual-level personality traits that are also predicted by pathogen prevalence.

The second hypothesis arises as a logical corollary of the first. Increased homozygosity that results from inbreeding necessarily compromises immune mechanisms that exploit molecular diversity to defend against parasites (Penn and Potts, 1999). This costly consequence of inbreeding manifests especially as an increased susceptibility to diseases caused by novel parasites. Thus, in contemporary human societies (in which contact with novel parasites is common as a result of the availability of modern transportation), the implication is that greater prevalence of consanguineous marriages will predict higher levels of morbidity and mortality from infectious diseases. This appeared to be the case as well. Additional analyses indicated that this effect occurred even when controlling for GDP per capita, and it also occurred regardless of the actual prevalence of parasites in the current local ecology.

Together, these findings illustrate the importance of distinguishing between the ecological circumstances present during the rise of human behavioral norms, and the ecological circumstances under which the behavioral norms exert their contemporary consequences, as they both impact on marriage patterns. Cross-cultural differences in mating and marriage norms typically have arisen over long periods of history during which populations were (in comparison to contemporary populations) relatively isolated and thus unlikely to come into regular contact with novel parasites. Under these ecological circumstances, inbreeding can be an adaptive behavioral strategy – especially in regions characterized by a high prevalence of parasites. Once the cultural norms arise, they can be persistent, even in the face of changing infectious disease stress. While inbreeding may have been adaptive under conditions of relative isolation of groups, it can have maladaptive immunological consequences in contemporary social ecologies in which contact with novel parasites is much more common.

Despite countless studies pertaining to the negative effects of inbreeding, our study indicates that, under certain circumstances (i.e., high pathogen prevalence), inbreeding may have advantages that outweigh its costs. Outside of humans, it is often assumed that

inbreeding is simply maladaptive and that non-human animals are adapted to avoid it altogether. We question this assumption. First, a wide range of species inbreed very closely with siblings. In these species, male–male competition for mates is highly localized. While Hamilton (1967) demonstrated that extreme inbreeding results in strongly female-biased sex ratios within broods, he did not address *why* the species involved show sibling mating. The only published general theory of inbreeding is not very specific: Shields (1982) posited that inbreeding has the benefit of keeping co-adapted gene complexes together and suggested that the presence of parasites may be one context that fosters the need for local co-adapted gene complexes. In line with this suggestion, we focus on parasites, because of the general localization of the co-evolutionary races of hosts and parasites. The literature on infectious diseases supports this localization in both hosts and their parasites (a good introduction is Thompson, 2005).

Hamilton (1967) also points out that populations are structured such that mating is not random across the population, but local in terms of genealogical descent (i.e., inbreeding), and that the localization of mating is variable across populations. Our hypothesis suggests that, to deal with local parasites, local mate competition is associated with adaptive inbreeding. This prediction could be tested by looking, across species, for the predicted positive relationship between parasite stress (or a suitable surrogate such as latitude; Guernier, Hochberg, and Guegan, 2004) and the degree of female-bias in broods of offspring (a correlate of inbreeding). This is a more feasible test than using comparative mate-preference behavioral data, because few data are available on inbreeding behavior in most species. Beyond Bateson's (1982) quail research that showed a first-cousin mate preference, there is scant literature on inbreeding preference at a relatedness of less than 0.25, especially close and distant cousin-level inbreeding. Possibly, this paucity of behavioral data reflects the bias in thinking that distant out-breeding is always the optimum. Finally, it is well known that, across plant species, there is a great range of close to distant inbreeding to extreme out-breeding, which may be related to the variation in infectious disease.

It is worth noting that our research results emerged despite limitations associated with the data set we used. Country-level measures of consanguinity are crude, as they average across differences that may occur between cultural and sub-cultural populations that exist within geopolitical borders. Pathogen prevalence and health outcomes also may vary widely within a country, depending on various geographical, meteorological, and socio-economic variables. The percentages of consanguineous marriages are from secondary sources and may not reflect accurately the prevalence of this type of union. Any such differences are likely to manifest in non-systematic measurement error, depressing the size of correlations. Thus, our results may actually underestimate the magnitude of relations between disease-relevant variables and human inbreeding.

It is interesting to consider the effect of historical pathogen prevalence on consanguineous marriage alongside other cross-cultural differences that are related to parasite prevalence. In regions that historically have had high levels of pathogen prevalence, people are less extraverted, less open to novel experiences, and have more restricted approaches to mating (Schaller and Murray, 2008). They also are more likely to endorse collectivist values that emphasize within-group interdependence, extended-family

nepotism, neophobia, xenophobia, and philopatry (Fincher and Thornhill 2008a, b; Fincher et al., 2008; Murray, Trudeau, and Schaller, in press; Thornhill et al., 2009; Thornhill, Fincher, Murray, and Schaller, 2010). All of these characteristics are conceptually consistent with increased inbreeding. Our results revealed little evidence that these traits and values are causally antecedent to consanguineous marriage. In fact, additional analyses revealed that correlations between consanguineous marriage and broader cultural values result, in part, from shared variance with pathogen prevalence. That is, the two measures of collectivism were correlated positively with consanguineous marriage, r 's = 0.314 and 0.290, but, when controlling for historical pathogen prevalence, these correlations were reduced, partial r 's = 0.215 and 0.092. Thus, while these broader traits and value systems may reinforce behavioral norms promoting inbreeding (and, in turn, be reinforced by inbreeding norms), somewhat distinct mechanisms may account for their emergence within the same ecologies. If so, it attests to the power of infectious diseases to impose selection pressures that are observed across many different levels of phenotypic analysis from immunological parameters to individual-level psychological traits to population-level cultural norms.

Received 18 May 2010; Revision submitted 2 November 2010; Accepted 3 November 2010

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Appendix

Table 1. Summary of consanguineous marriage data

Region	Weighted mean consanguineous percentage	Weighted mean coefficient of inbreeding	Historical pathogen prevalence (z-score)	World region	GDP per capita (2009-\$US)
Afghanistan	55.4	0.0332	0.23	West Eurasia	27.01
Algeria	22.6	N/A	0.47	Africa	241.4
Argentina	0.549	0.0003	-0.12	South America	548.8
Australia	0.474	0.00018	-0.25	Insular Pacific	851.1
Bahrain	44.40	0.016534	0.10	West Eurasia	28.31
Bangladesh	10.50	0.004491	0.62	East Eurasia	241.1
Belgium	1.061	0.000339	-1.00	West Eurasia	383.4
Bolivia	1.682	0.000262	0.34	South America	45.56
Brazil	4.348	0.002155	0.93	South America	2013
Burkina Faso	65.8	0.0355	1.16	Africa	18.81
Canada	1.508	0.000606	-1.31	North America	1279
Chile	.874	0.000611	-0.45	South America	242.2
China	4.952	0.02971	1.03	East Eurasia	8748
Colombia	3.49	0.0012	0.27	South America	401.5
Costa Rica	3.4	0.0011	0.12	South America	48.51
Croatia	0.10	N/A	-0.44	West Eurasia	78.57
Cuba*	0.80	0.0005	0.00	North America	110.9
Czech Republic	0.20	N/A	-0.87	West Eurasia	254.1
Ecuador	3.512	0.001335	0.34	South America	108.8
Egypt	31.015	0.012151	0.44	Africa	469.8
El Salvador	4.90	0.0014	0.30	South America	43.27
France	0.806	0.00236	-0.46	West Eurasia	2097
Guinea	25.90	0.0131	1.06	Africa	10.16
Honduras*	3.4	0.0011	0.16	South America	32.5
Hungary	0.14	0.00011	-1.00	West Eurasia	181.9
India	26.638	0.026427	0.94	East Eurasia	3570
Indonesia	17.80	0.0095	0.63	Insular Pacific	962.5

Adaptive and maladaptive human inbreeding

Iran	32.187	0.018204	-0.15	West Eurasia	827.1
Iraq	34.254	0.022192	0.54	West Eurasia	110
Ireland (Republic)	0.567	0.000229	-0.45	West Eurasia	172.5
Israel	20.032	0.012933	0.52	West Eurasia	205.8
Italy	0.591	0.000413	0.16	West Eurasia	1739
Japan	7.627	0.003215	0.43	East Eurasia	4150
Jordan	31.562	0.019107	0.16	West Eurasia	32.41
Kuwait	51.729	0.020535	-0.34	West Eurasia	142.1
Lebanon	26.595	0.14552	0.36	West Eurasia	53.98
Libya	37.6	0.0209	0.04	Africa	85.04
Malaysia	7.60	N/A	0.50	East Eurasia	383.6
Mexico	0.837	0.0003	0.28	North America	1465
Morocco	19.90	0.0089	0.59	Africa	145.6
Netherlands	0.200	0.0001	-0.87	West Eurasia	660
Nigeria	51.20	0.0242	1.16	Africa	339
Northern Ireland	0.671	0.0001	-0.87	West Eurasia	N/A
Norway	0.477	0.000231	-0.85	West Eurasia	267.4
Oman	35.876	0.016909	-0.14	West Eurasia	72.88
Pakistan	50.97	0.02150	0.02	East Eurasia	433.1
Panama	1.663	0.00	0.09	South America	40.81
Peru	2.472	0.001618	0.23	South America	251.4
Philippines	0.40	N/A	0.50	Insular Pacific	324.4
Portugal	1.56	0.000909	0.47	West Eurasia	232.6
Puerto Rico	3.30	0.0013	0.07	North America	67.82
Qatar*	44.50	0.0271	-0.25	West Eurasia	99.59
Saudi Arabia	38.357	0.021568	0.04	West Eurasia	592.3
Singapore	3.60	0.000345	0.31	East Eurasia	243.2
Slovakia	11.618	0.011567	-1.00	West Eurasia	115.1
Slovenia	0.60	N/A	-0.87	West Eurasia	55.46
South Africa	2.79	N/A	0.11	Africa	505.3
Spain	2.013	0.000628	-0.05	West Eurasia	1362

Adaptive and maladaptive human inbreeding

Sri Lanka	21.50	0.0092	0.64	East Eurasia	96.6
Sudan	50.379	0.023287	1.00	Africa	92.65
Sweden	0.653	0.00038	-0.98	West Eurasia	331.4
Syria	31.609	0.023322	0.30	West Eurasia	101
Tajikistan*	20	0.0022	0.02	East Eurasia	13.67
Tanzania	37.80	0,0236	0.75	Africa	57.69
Tunisia	26.90	0.0213	0.81	Africa	86.35
Turkey	20.137	0.007681	0.16	West Eurasia	874.5
Turkmenistan	N/A	0.010688	0.00	West Eurasia	32.56
United Arab Emirates	35.99	0.0159	-0.45	West Eurasia	186.6
United States	0.193	0.000121	-0.89	North America	14140
Uruguay	2.1	0.000973	0.39	South America	43.94
Venezuela	1.385	0.000615	0.48	South America	349.3
Yemen	34.949	0.021511	0.41	West Eurasia	58.04

Note: For regions marked with *, historical data on either leprosy and/or tuberculosis were unavailable. The overall pathogen prevalence index was computed as the mean *z*-score of the seven remaining diseases.